



## Zika—a new continent and new complications?

The latest reminders that we live in a medically connected global community are the appearance of the Africa-born Zika virus infection in Brazil and other areas within the Western hemisphere and the subsequent apparent transmission of the disease to female sexual contacts of infected males in the United States. Zika virus' geographic travels are most certainly of interest; they can be traced from sub-Saharan Africa, where serologically identified outbreaks have continued since 1947, through Asia, Micronesia, Polynesia, and now South and Central America. But what may turn out to be even more interesting than the virus's travel itinerary is what we may learn about the Zika virus-human host interaction and the subsequent spectrum of clinical disease.

The primary clinical illness following serologically defined infection seems to be relatively uncommon and generally mild: a fairly nondistinctive febrile episode with mild rash, small- and large-joint arthralgias or arthritis, and nonpurulent conjunctivitis. But what has fostered the greatest concern is the epidemiologic association of Zika infection with the neurologic complications of microcephaly and Guillain-Barré syndrome (GBS).

During the 2013–2014 outbreak of Zika infection in French Polynesia, 42 patients with GBS were identified, 100% of whom had serologic evidence suggestive of recent Zika infection, compared with 56% of control patients without GBS.<sup>1</sup> Serologic determination of recent infection can be difficult due to cross-reactivity with other flaviviruses, but it seems that in the Polynesian outbreak the risk of GBS might be much less than 1 in 1,000 patients. This is not unlike the incidence of GBS following influenza, *Campylobacter*, and cytomegalovirus. One explanation for why GBS may follow certain infections is that the infection can trigger antibodies that cross-react with neuronal membrane components. However, those antiganglioside antibodies were not uniformly present in the Polynesian patients who developed GBS following Zika infection. Thus, this may provide an opportunity to further understand the mechanism by which GBS is associated with some infections, in selected patients.

Patients with post-Zika GBS seem to fare well, with a very good prognosis for complete recovery. That is not the case, however, for infants born with microcephaly, another epidemiologically linked complication of Zika infection. In Brazil, the exact incidence rate remains to be determined, and it is not yet certain whether the rate is higher than in the previous Polynesian epidemic (the number of infections is far greater in Brazil, and thus the accuracy of estimated frequency may also be greater), but there may have been a significantly increased frequency of microcephaly in the Polynesian outbreak as well. Like the related West Nile, Saint Louis encephalitis, and Japanese encephalitis viruses, Zika virus has the ability to directly attack certain neurons, and the Zika genome has been detected in brains of infected babies at autopsy. So this particularly devastating aspect of Zika infection may turn out to be relatively

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easy to understand—perhaps the portal for viral infection of specific neurons is expressed only at certain times during brain development. I'm sure these investigations are under way at a feverish pitch.

Recognizing that new information is being released virtually daily, Flores et al (page 261 in this issue of the *Journal*) provide a current overview of our understanding of the virus and some practical advice regarding diagnosis and prevention.

As laboratories gear up to devise rapid and more specific diagnostic tests and develop effective anti-Zika vaccines, we hope to learn more about how a seemingly minimally relevant virus, when introduced into a new environment, can wreak clinical havoc. Possible explanations abound—genetic differences in the population, altered immunologic background of infected patients due to prior infection with related viruses such as dengue, or the direct impact of other coinfections. Or, with careful study, it may be discovered that these neurologic issues have been present elsewhere all along, but not previously linked to the Zika virus.



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1. Cao-Lormeau VM, Blake A, Mons S, et al. Guillain-Barré syndrome outbreak associated with Zika virus infection in French Polynesia: a case-control study. *Lancet* 2016 Feb 29. pii: S0140-6736(16)00562-6. doi: 10.1016/S0140-6736(16)00562-6. [Epub ahead of print].